UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

AUG 15 2016

MEMORANDUM

SUBJECT: **Section 18 - Specific Exemptions** for the Use of Streptomycin (EE# 16FL02) and Oxytetracycline (EE# 16FL03) in Florida Citrus Infected with Huanglongbing or Citrus Greening Disease (*Candidatus Liberibacter asiaticus*)

FROM: Michael L. Goodis, Acting Director
Registration Division
Office of Pesticide Programs

8/9/16

TO: Jack E. Housenger, Director
Office of Pesticide Programs

I. APPLICANT REQUEST

APPLICANT: Florida Department of Agriculture and Consumer Services

CHEMICALS: Streptomycin Sulfate (CAS No. 3810–74–0)
Oxytetracycline Calcium (CAS No. 7179–50–2)
Oxytetracycline Hydrochloride (CAS No. 2058–46–0)

PRODUCTS: **FireWall™ 50WP** (EPA Reg. No. 80990-3, containing 65.8% streptomycin sulfate, (equivalent to 50% streptomycin), manufactured by AgroSource, Inc.
FireLine™ 17WP (EPA Reg. No. 80990-1, containing 18.3% oxytetracycline hydrochloride, (equivalent to 17% oxytetracycline) manufactured by AgroSource, Inc.
Mycoshield® (EPA Reg. No. 55146-97, containing 31.5% oxytetracycline calcium, (equivalent to 17% oxytetracycline), manufactured by NuFarm Americas, Inc.

SITES: Orange and grapefruit crop subgroups (Grapefruit, lemon, lime, orange, tangelo, tangerine, citrus citron, kumquat, and hybrids of these, plus pummelo

PEST: Huanglongbing, also known as Citrus Greening Disease (caused by the bacteria, *Candidatus Liberibacter asiaticus,* vectored by the Asian citrus psyllid)

USE PATTERNS: **FireWall™ 50WP (Streptomycin sulfate)**: Three foliar applications by ground airblast spray at 11 oz. product (0.45 lb. a.i. streptomycin sulfate) per acre; re-treatment interval of 21 days; maximum of 33 oz. of product (1.35 lb. a.i. streptomycin sulfate), per acre per year; 40-day PHI.

FireLine™ 17WP (Oxytetracycline hydrochloride): Three foliar applications by ground airblast spray at 1.5 lb. product (0.255 lb. a.i. oxytetracycline) per acre; re-treatment interval of 21 days; maximum of 4.5 lb. product (0.765 lb. a.i. oxytetracycline) per acre per year; 40-day PHI.

Mycoshield® (Oxytetracycline calcium complex): Eight foliar applications by ground airblast spray of a 200-300 ppm solution (equivalent to 1 – 1.5 lb. product or 0.17 to 0.255 lb. a.i. oxytetracycline); retreatment interval of 21 days; maximum of 8-12 lb. product (1.36 – 2.04 lb. a.i. oxytetracycline) per acre per year; 21-day PHI.

For the oxytetracycline products: Two products are being requested with two different use patterns based upon each registrants' research and recommendations. However, each set of use directions contains the restriction that no more than 2 lb. a.i. oxytetracycline may be applied per acre per year as total contributed from all products applied.

ACREAGE: A maximum of 388,534 acres of citrus fruit in Florida may be treated

USE SEASON: Now until December 31, 2016

II. EMERGENCY SITUATION AND ALTERNATIVES:

According to the Florida Department of Agriculture and Consumer Services (FDACS), citrus growers have a critical need for tools to manage Huanglongbing (HLB, or citrus greening) disease. There are currently no EPA-registered bactericides for prevention of infection or suppression of HLB, or for the improvement of tree health of infected trees. FDACS states that this urgent and non-routine situation has caused significant losses in production, yield, acreage, and jobs, and will affect the long-term economic viability of Florida's $8.9 billion citrus industry if not alleviated.

The disease is caused by the bacteria *Candidatus Liberibacter asiaticus* (CLas) and is vectored by the Asian citrus psyllid (ACP), an invasive pest first discovered in Florida in 1998. Worldwide, HLB is considered the most serious disease of citrus and has greatly limited commercial production in countries where it is present. HLB was first documented in Florida in 2005 and by 2009 had spread to 33 counties in Florida comprising nearly 80% of the Florida peninsula.

The HLB bacterium lives in the phloem (circulatory system) of the tree causing decline and eventual death of the tree. The long latency period of HLB has made predicting or managing the disease particularly difficult since infected trees are often non-symptomatic, providing a source of infection to other trees. The disease begins with yellowing leaves, progressing to defoliation, reduced fruit production, and misshapen fruit exhibiting "greening" (failure to color properly). Additionally, excessive premature fruit drop occurs, reported at over 10% in all varieties over the past 3 years. Further, the fruit produces bitter juice, reducing economic value. Ultimately, the HLB disease kills the tree.

Despite producers employing all the best available strategies and tools (control of ACP, nutritional support of the tree, and removal of diseased trees), the disease has continued to spread, forcing a large number of farmers out of the industry, with many more to follow if no relief is available soon.

FDACS states that projected production for 2016 is the lowest since 1964, and although new citrus trees have been planted at a higher-density, Florida citrus has seen a drop of 58% in production, 42% in yield, and over 30% in acreage planted over the last decade, primarily due to HLB. Estimates from 2012 indicate that HLB has caused over $7 billion in lost revenue and loss of thousands of jobs. FDACS states that access to viable management options are critical at this point in time.

Recent research on using antimicrobial agents has suggested that, while not curative, some recovery of infected trees was observed, which is expected would increase tree health, and ultimately extend the life of viable production of the tree. While realizing that use of antibiotics is not a long-term solution, FDACS has submitted the requests for use of streptomycin and oxytetracycline under emergency exemptions in hopes of providing a measure of relief until more sustainable solutions are developed. Research is ongoing to develop tolerant/resistant citrus varieties and although results have been promising, it will be a number of years before these varieties are available for commercial production. Even at such a point, the time will be needed for the trees to grow, mature, and reach viable production. Research into other control materials and methods is also ongoing.

FDACS states that without the requested antibiotic tools to help manage this disease, infected trees will no longer be economically productive within 5 to 8 years of infection. With the rapid decline of HLB-infected mature trees and falling yields, Florida's citrus is nearing a critical point where the supplies of fruit may become inadequate to sustain Florida's juice-processing infrastructure (90% of FL citrus is for juice), which employs over 75 thousand workers. Economic analysis for currently planted young citrus trees indicates that losing as few as five percent of this acreage to HLB will result in lost viability of long-term production.

BACKGROUND

This is the first year that requests for emergency exemptions under FIFRA section 18 have been submitted for use of streptomycin and oxytetracycline for managing HLB in citrus. Unrelated exemptions have been authorized for use of streptomycin to control citrus canker on fresh market grapefruit in Florida for the past three years. Streptomycin and oxytetracycline are both registered on a number of sites, including uses on apple, pear, peach, and nectarine with use patterns similar to those being requested on citrus.

Crisis Exemption: On March 4, 2016, FDACS, after consulting with EPA, declared a crisis exemption to authorize the uses as proposed in their specific exemption request. Additional detail on that process may be found below in the "Notice of Receipt" section.

Progress Toward Registration: Tolerance petitions have been submitted to EPA for both chemicals. The oxytetracycline petition (PP# 5F8415) was received in October 2015 and has a PRIA date of February 2017. The streptomycin petition (PP# 5F8427) was received in December 2015 and has a PRIA date of April 2017.

Notice of Receipt/Public Comment: In accordance with 40 CFR 166.24(a)(8), a notice of receipt allowing public comment published in the Federal Register on January 27, 2016 (81 FR 4624) since the applicant proposed uses of materials also used as human and animal antibiotics. The comment period closed on February 11, 2016. A total of 70 comments were received.

Sixty-four comments were received in favor of allowing the uses, with 40 representing producer and industry groups. Of particular note were comments received from USDA/ARS and IR-4 outlining rationale for authorization of the uses. USDA noted their involvement and support in research toward finding a long-term solution, including exploring efficacy of antibiotic materials.

Six comments were received opposing the uses. Two of these were anonymous, one was from an individual microbiology post-graduate student concerned about resistance developing and 3 were from the following public interest organizations: Keep Antibiotics Working (KAW), Natural Resources Defense Council (NRDC), and Food and Water Watch (FWW). The most detailed was from KAW, a coalition of advocacy groups active in lobbying against the inappropriate antibiotic use in food animals. NRDC and FWW comments indicated support of the submission from KAW. They expressed concern that the use would lead to resistance development which could impact human health. They were also concerned by what they perceive as the lack of public participation and potential haste to allow the use, citing the 15-day public comment period as insufficient. Additionally, they were concerned that non-pesticidal alternatives were not being adequately considered.

EPA acknowledges the concerns expressed in the comments regarding increased risk of resistance developing in microbes from greater exposure to antibiotics in the environment. EPA also notes a need to balance potential risks with the severity of the emergency situation and potential benefits for alleviating the situation. Taking these and other factors into consideration, ***EPA concurred upon FDACS crisis declaration for these uses, based on the following:***

- EPA believes that the situation faced by Florida citrus producers is a valid and urgent emergency because the citrus industry has been severely impacted by the disease.
- EPA believes that the potential benefits are significant and may make the difference between staying or going out of business for many producers; the viability of the entire Florida citrus industry may be at risk without some way of managing HLB.
- Recognizing that these exemptions are temporary solutions, EPA supports research toward development of sustainable management solutions to maintain the viability of Florida's citrus industry.
- Monitoring for resistance in microbes that inhabit the treated orchards will be an integral part of the exemption program in Florida with frequent updates provided to EPA.
- The United States Department of Agriculture (USDA) and IR-4 have supported research of these uses and other potential solutions to the HLB management in citrus in the United States. These organizations have given valid arguments in support of these uses which EPA has also taken into consideration.

III. EPA EVALUATIONS

BIOLOGICAL AND ECONOMIC ANALYSIS

The Biological and Economic Analysis Division (BEAD) reviewed Florida's emergency exemption requests and determined that the introduction and rapid spread of the HLB pathogen vectored by the ACP and subsequent reduction in tree-health and production, is an urgent and non-routine situation. Although the introduction of HLB was recognized over a decade ago, no effective management of the disease has been identified or developed. Management of HLB in Florida has focused largely on controlling the ACP vector, with little success, while this submission requests use of antibiotics to suppress the disease itself. BEAD concluded that there are no effective available alternatives for suppression of HLB in citrus trees in Florida, and that citrus growers in Florida are likely to experience significant economic losses due to HLB.

Biological Analysis: Florida has requested use of two antibiotics under emergency exemptions as part of a three-pronged approach to manage HLB: 1) manage the ACP vector; 2) access to antibiotics that improve tree health and prolong the production viability of infected trees, and 3) breed new citrus trees that will tolerate or resist HLB. This is the first time a use has been proposed which will focus on managing the disease organism rather than the vector. BEAD noted that the request included data from recent research conducted in 2014-15 at 17 Florida field locations which show that foliar applications of streptomycin and oxytetracycline resulted in statistically significant reductions of CLas titer in HLB-infected trees. Furthermore, these studies indicated reduction in HLB symptoms and statistically significant improvements in tree-health, such as increased canopy density, reduced leaf drop and branch dieback, reduced fruit drop, and increased fruit load. These results suggest that the use of bactericides may increase tree health and improve production in trees that are already experiencing symptoms of HLB-infection. BEAD also noted that more research is planned for 2016 to further explore improvements in tree vigor following the application of bactericides. BEAD indicates that both oxytetracycline and streptomycin would likely need to be used in conjunction to provide consistent benefits throughout the season, with neither being sufficient on their own; thus a request for use of two materials to be used in rotation is justified.

***Economic Analysis*:** BEAD concluded that growers currently have no viable options for management of this disease. Even incorporating best management practices and other available treatments, potential yield losses from HLB are well above the 20% threshold to qualify as a significant economic loss in the affected trees and orchards. Further, potential yield loss for bearing trees is 100%, because the disease ultimately causes the complete loss of the tree. Additional losses occur when infected trees must be removed while still productive, in order to reduce spread of HLB. Lowered quality also results in decreased prices or unusable fruit, further impacting grower revenues. Survey results from Florida citrus growers showed substantial losses from decreased yield in remaining trees, as well. A 2015 survey of citrus growers reported the average loss in yield to HLB of 40%. BEAD noted that this is consistent with changes in yield measured statewide according to USDA figures. Comparing the average yield from the most recent five years to that from the five-year period before HLB was identified, showed substantial reductions, as follows: for 2000-04, orange yield of 384 boxes per acre fell by 35% to 291 boxes per acre for 2011-15; and comparing the same time periods, grapefruit yields decreased by 17%. Note that these yield losses measure only the yield from surviving trees, while removed trees or abandoned orchards represent additional losses (but are not included in the USDA yield

measures). Citrus acreage in Florida has fallen over 31% from 749,000 acres in 2004 to 515,000 acres in 2014. Based upon this information, BEAD concludes that the emergency situation caused by HLB in Florida will result in significant economic loss to citrus producers in that state.

HEALTH EFFECTS RISK ASSESSMENT

The Health Effects Division (HED) conducted exposure and risk assessments for the proposed emergency uses of oxytetracycline and streptomycin. The findings for each are presented in the following section.

Oxytetracycline:

The residue of concern is the parent compound, oxytetracycline, and adequate residue data were submitted to support the proposed emergency exemption uses. Two different compounds, oxytetracycline hydrochloride and oxytetracycline calcium, were proposed for use, with the use pattern for the calcium compound having the higher rate and shorter PHI. Therefore, HED used the data from the oxytetracycline calcium use pattern to determine a **recommended tolerance of 0.4 ppm for all citrus commodities; separate tolerances are not required for any of the processed citrus commodities.**

Based on the information available on the effects of oxytetracycline in humans, supplemented with the data available on the toxicity of oxytetracycline in laboratory animals, the toxicology database is considered complete and sufficient to evaluate toxicity.

An acute dietary endpoint was not identified since no effects were attributable to a single dose. Based upon this and the reported history of safe use in humans as a drug, an acute dietary assessment was not indicated. Oxytetracycline is classified as Group D with respect to cancer risk concerns (D "not classifiable as to human carcinogenicity") and therefore a cancer risk assessment was not required. No evidence of neurotoxicity has been observed in any study. The results from the developmental studies and information did not indicate increased sensitivity from pre- and/or post-natal sensitivity; therefore the FQPA safety factor is reduced to 1X.

Chronic toxicity was characterized using the NOAEL of 100 mg/kg/day from rat and dog chronic feeding studies (minor effects seen of decreased body weight). Incorporating a 100X uncertainty factor, the cPAD was determined to be 1 mg/kg/day. The chronic dietary risk assessment used 100% crop treated for all uses, tolerance level residues including those for livestock commodities from animal drug uses, and default processing factors (except for citrus juice, citrus oil, citrus peel). The estimated dietary exposures (food plus drinking water) occupied **1.4% of the cPAD for the US. Population, and 4% of the cPAD for the most highly exposed subpopulation, children 1-2 years old. All other chronic dietary risk estimates are also less than 100% of the cPAD and therefore not of concern.**

Based upon available data, the low systemic toxicity, and the low exposure potential relative to pharmaceutical uses, no incidental oral, inhalation or dermal endpoints have been identified and oxytetracycline does not meet the EPA's toxicity criteria that would trigger the requirement of occupational or residential exposure risk assessment. The potential for worker exposure is mitigated by the PPE proposed (long-sleeved shirt; long pants; chemical-resistant gloves; shoes plus socks; protective eyewear; A NIOSH-approved particulate respirator with any N, R, or P filter with NIOSH approval number prefix TC-84A; or a NIOSH-approved powered air purifying

respirator with an HE filter with NIOSH approval number prefix TC-21C; chemical-resistant headgear ensuring full coverage of the neck. Further, a 12 hour REI will reduce post-application exposures. **The estimated aggregate exposure risks are represented by the chronic dietary exposure and risk estimations (food plus drinking water), which were previously discussed.**

In summary, HED determined that there are no hazard, residue chemistry, dietary or occupational/residential considerations that would preclude granting the requested exemption for oxytetracycline and establishing the supporting time-limited tolerances.

Streptomycin

The residue of toxicological concern is the parent compound, streptomycin, and acceptable data were submitted for the purposes of the section 18 use to support establishing the recommended tolerances **for streptomycin in/on citrus fruit at 2 ppm and on citrus dried pulp at 6 ppm, based upon a 40-day PHI**. *(HED-recommended tolerances higher than those proposed by FDACS since they amended the proposed use from a 60-day to a 40-day PHI.)*

All toxicological data requirements have been waived for streptomycin because of the extensive database in humans and animals from clinical use, along with assessments conducted by the Food and Drug Administration (FDA) and published literature. The database is considered complete and the existing body of data sufficient to evaluate toxicity of streptomycin.

An acute dietary endpoint was not identified since no effects were observed from a single dose. Based upon this and the history of safe use in humans as a drug, an acute dietary assessment was not indicated.

Due to the lack of guideline studies (because of data waivers), streptomycin was classified as "Inadequate Information to Assess Carcinogenic Potential." However, the 2 year rat carcinogenicity study used by FDA and World Health Organization (WHO), to estimate risks from residues in animal products from use as an animal drug, did not demonstrate evidence of carcinogenicity. Also, the literature available for streptomycin toxicity in animals and humans does not contain any indication of carcinogenicity. Based upon this, a cancer risk assessment was not required. Additionally, the extensive database for streptomycin does not contain any evidence of neurotoxicity. No teratogenic effects were observed in the rabbit developmental study and there is no direct evidence of pre- and/or post-natal sensitivity; therefore, the FQPA safety factor is reduced to 1X.

For risk assessment purposes, the endpoint for chronic dietary, incidental oral, and inhalation exposures is based upon the NOAEL of 5 mg/kg/day from a 2-year feeding study in rats with an effect of reduced body weight gain, the only adverse effect noted. Incorporating a 100X uncertainty factor, the cPAD was determined to be 0.05 mg/kg/day.

The chronic dietary risk assessment used 100% crop treated for all uses, tolerance level residues including those for livestock commodities from animal drug uses, and default processing factors (except for citrus juice, citrus oil, citrus peel, and tomato puree). The estimated dietary exposures (food plus drinking water) occupied **40% of the cPAD for the US. Population, and 90% of the cPAD for the most highly exposed subpopulation, all infants (<1 year old). All other chronic dietary risk estimates are less than 100% of the cPAD and therefore not of concern.**

Streptomycin is registered for residential uses on gardens and trees and exposures and risk was assessed for inhalation exposure of handlers. Available data indicate dermal absorption is low; thus toxicity from dermal exposure is not expected was not assessed. Further, residential post-application exposures are assumed to be negligible from non-dietary ingestion and inhalation. Risks were estimated for inhalation exposures of handlers during residential use, and for all scenarios, the lowest MOE was 86,000 (LOC is ≤ 100). **Therefore, residential risk estimates are not of concern.**

A short-term aggregate assessment was conducted based on dietary and inhalation exposures. The highest dietary exposure (for the population subgroup of adults 20-49 years old) and the residential scenario resulting in highest exposure (handler using handwand/backpack), were used to assess aggregate risks; the short-term aggregate MOE was determined to be 270 (LOC is ≤ 100). Residential exposure is not quantitatively assessed for children, so their aggregate exposure risks are represented by the chronic dietary risk estimates, which were previously discussed and not of concern. **Therefore, aggregate exposure estimates are not of concern.**

Occupational exposure and risks were estimated for the scenario proposed by FDACS (airblast application by ground equipments). The potential for worker exposure is mitigated by the PPE proposed (long-sleeved shirt; long pants; chemical-resistant gloves; shoes plus socks; protective eyewear; A NIOSH-approved particulate respirator with any N, R, or P filter with NIOSH approval number prefix TC-84A; or a NIOSH-approved powered air purifying respirator with an HE filter with NIOSH approval number prefix TC-21C; chemical-resistant headgear ensuring full coverage of the neck) Further, a 12 hour REI will reduce post-application exposures. **Therefore, HED concluded that occupational risks estimates are not of concern for all scenarios considered, with the lowest MOEs at 3,400.**

In summary, HED determined that there are no hazard, residue chemistry, dietary or occupational/residential considerations that would preclude granting the requested section 18 exemption for streptomycin and establishing the recommended time-limited tolerances.

ENVIRONMENTAL FATE AND EFFECTS ASSESSMENTS

The Environmental Fate and Effects Division (EFED) conducted exposure and risk assessments for the proposed emergency uses of oxytetracycline and streptomycin. The findings for each are presented below.

Streptomycin

OPP's Environmental Fate and Effects Division (EFED) reviewed the requested use and stated that their findings rely upon the recent (7/22/15) section 3 new use environmental fate and ecological effects risk assessment for the proposed new uses on grapefruit and tomatoes. EFED stated that while the application parameters for the Florida emergency exemption differ somewhat from those assessed in the 7/22/15 document, the EECs for the proposed use are similar to those calculated for the tomato scenario. Therefore the results and risk conclusion from that assessment would apply to this use. Additionally, it is noted that the proposed rate for this emergency exemption is lower than the maximum rate currently registered for use on apples and pears of 0.67 lbs a.i./A (1 application) and a maximum seasonal rate of 6.05 lbs a.i./A.

Based upon the 7/22/15 risk assessment, EFED concluded that the proposed use of streptomycin on citrus results in potential risk to mammals from chronic exposure (RQ = 11.6) and risk to sensitive aquatic nonvascular plants (RQ = 3.2). EFED notes that the toxicological endpoint used for risk to mammals was from the 2-year rat study used by HED. That study indicated that the only adverse effect seen was reduced body weight gain. No other taxa are thought to be at risk from this use.

Oxytetracycline

EFED reviewed the proposed use of oxytetracycline and concluded that oxytetracycline is practically non-toxic to both terrestrial and aquatic organisms on an acute basis, and acute RQ values were not calculated since acute risks for non-target animals were considered low. Further, EFED stated that since all toxicity endpoints (acute and chronic) are several orders of magnitude greater than the EEC of 93.4 ug/L the likelihood of either acute or chronic risk to aquatic organisms is considered low. Additionally, it should be noted that the EEC used for the assessment is based upon the oxytetracycline use in apples, a higher rate than that proposed for citrus.

Chronic RQ values for birds ranged from <0.01 to 0.27 depending upon size and diet, and are below the chronic risk level of concern (LOC) of 1.0. The RQ values for mammals range between <0.01 to 0.06, also below the chronic LOC. However, since the chronic toxicity endpoint for mammals was not determined (LOAEL was the lowest dose tested, 1,200 mg/kg/day from the rat developmental study with the effect of decreased fetal body weight) there is some uncertainty regarding effects on mammals.

With respect to potential risks to terrestrial invertebrates, oxytetracycline is classified as practically non-toxic to honey bees on an acute contact exposure basis. While EFED did not have specific studies on acute or chronic toxicity to larval bees or the chronic toxicity to adults, oxytetracycline is used in bee colonies to control several diseases in honey bee larvae without apparent adverse effects to either adult or larval bees.

Risks to Listed Species

EFED stated that federally listed threatened and endangered species are co-located in the proposed application areas, including the following five species of mammals: Southeastern Beach Mouse (*Peromyscus polionotus niveiventris*), Florida Panther (*Puma concolor coryi),* West Indian Manatee including two distinct subspecies, *i.e.*, the Florida Manatee (*Trichechus manatus latirostris*) and the Antillean Manatee (*T. manatus manatus*), and the Florida Bonneted Bat (*Eumops floridanus*). EFED noted that the FDACS submission asserted that the proposed uses would not present risks of concern based upon additional restrictions expected to minimize exposure to nontarget organisms. In particular, the use patterns proposed by FDACS include a limited total amount of oxytetracycline per year, no aerial applications, no applications in groves with animal manure fertilization (to reduce development of antibiotic-resistant enteric bacteria), and prohibit applications on and near water sources. EFED notes, however, that there is some uncertainty regarding potential impacts to listed mammals given the non-definitive NOAEL. As noted earlier, absolute RQ values for mammals are well below the chronic risk LOC and actual RQs are non-definitive and potential risk cannot be precluded. However EFED stated that exposure is likely to be minimal for each of the species, which renders potential risks as discountable. For the three terrestrial spp. EFED states that the potential for overlap of essential

habitat with areas proposed for citrus greening control is considered minimal. As for the one aquatic spp (West Indian manatee), EFED stated that given the restrictions on aerial applications and any direct applications to water, the likelihood of exposure to manatees is also low. EFED also notes that since the proposed uses have maximum rates lower than that previously evaluated and the conclusions regarding potential ecological risks remain the same, the proposed uses do not appear to represent risks to nontarget organisms.

OPP'S REVIEW BASED ON FDA GUIDANCE 152:

For new requests for pesticide uses of antibiotics, OPP completes an evaluation to assess the risk of potential contribution to resistance development in human pathogens. This review is based upon FDA Guidance 152 which addresses the expansion of human antibiotics to the veterinary arena. OPP has adapted the procedure to fit expansion of antibiotic use through use as pesticides. The review consists of three elements discussed below, which together provide the information to make an overall qualitative risk estimate. These findings are then shared with officials from Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) for their reaction and feedback. The following summarizes the results:

Release assessment: probability that resistant bacteria are present on food commodities as a result of antibiotic use on crops. The release assessment rating for the proposed section 18 use was given a ***"high determination"***. The 152 Review Team stated that CDC and FDA have recently indicated that widespread selection of multidrug resistance plasmids within the Enterobacteriaceae family of bacteria have led to an explosion of infections with carbapenem resistant Enterobacteriaceae (CRE) pathogens recalcitrant to most antibiotic treatments. (Carbapenems are antibiotics used against multi-drug resistant pathogens.) Large-scale environmental release, as requested, would increase selection pressure to favor the multidrug resistance plasmids in CRE as well as other environmental bacteria.

Exposure assessment: probability that humans would ingest or be exposed to bacteria from the treated food commodity. The exposures resulting from the proposed Section 18s were given a ***high determination***. The 152 Review Team stated that this is based upon the large acreage and type of application being less controlled (airblast by ground). The added that an additional factor considered is the perceived limited efficacy of requested materials.

Consequence assessment: probability that the exposure to resistant bacteria could result in an adverse health consequence. The consequence assessment rating for the proposed section 18 uses was given a ***High determination.*** The 152 Review Team indicated that this is based partly upon information from CDC which indicated recent approval of several new antibiotics, particularly one for control of CRE (e.g., *E.coli, Klebsiella,* and *Salmonella*) could be jeopardized by larger environmental release of streptomycin.

Overall Qualitative Risk Estimate: Overall level of concern: ***High***. This results from a "High" classification for both the release and exposure risk estimates and the "Highly Important" consequence classification.

CDC and FDA Feedback:

The review was shared with FDA and CDC who were requested to provide their feedback, and was then discussed during a conference call. Concern was expressed based on several factors. The expansive area to potentially be treated was of concern. They also expressed concern about the uncertain efficacy showing only suppression of the disease but no indication of how this would ultimately impact production. They are concerned that the materials would be applied prophylactically in areas with no incidence of HLB. CDC also indicated that since the initial approvals of antibiotics for agricultural uses, there has been a huge shift in opinions on expanded antibiotic use and concern for resistance; there is consequently a much greater concern now for new uses as well as existing (based in part by increase in CRE pathogens and occurrence of multidrug resistance plasmids and concern of transfer to other bacterial species.) Also concern for cross-resistance development in human pathogens to entire classes of antibiotics (and impact upon newly cleared antibiotics). CDC also noted that allowing the proposed uses may run counter to recent FDA updates to guidance aimed at limiting farm use of antibiotics to only those animals which are veterinarian-verified to be sick or to have been exposed to other sick animals.

Bacterial Resistance Risk Mitigation and Monitoring: EPA acknowledges the concerns associated with the use of antibiotics contributing to resistance in environmental microbes and the potential impact to human and animal pathogens. Extensive monitoring for resistance among endemic microbes in orchards will be required. CDC and FDA will be consulted for input as to methods and data to be gathered under the monitoring program. Additionally, FDACS indicates that good stewardship practices such as rotating chemistries and ensuring that reservoirs of the disease (such as abandoned orchards) are destroyed are high priorities.

EPA will require the following modifications to help mitigate risks for resistance development and these will appear on the use directions for all three products:

- Do not apply at any rate below that specified in these use directions.
- Do not apply in groves in which current practices include fertilization with raw animal manure. This restriction addresses concerns that *{oxytetracycline / streptomycin}* resistance could be transferred to *E. coli* or other pathogenic bacteria in the manure.
- When feasible, ***{PRODUCT NAME}*** should be alternated with a comparable bactericide with a different mode of action to reduce risks of selecting for *{oxytetracycline / streptomycin}* - resistant organisms.

To reduce worker exposures, thereby reducing exposure to microbes of human origin, to help mitigate risks for resistance development, EPA will require the following modifications, which will appear on the use directions for all three products:

- Chemical-resistant gloves
- Protective eyewear (goggles, face shield, or safety glasses)
- A NIOSH-approved particulate respirator with any N, R, or P filter with NIOSH approval number prefix TC-84A; or a NIOSH-approved powered air purifying respirator with an HE filter with NIOSH approval number prefix TC-21C.
- Chemical-resistant headgear ensuring full coverage of the neck

IV. RECOMMENDATION:

I recommend that specific exemptions be granted to the Florida Department of Agriculture and Consumer Services (FDACS) for the uses of oxytetracycline and streptomycin in management of HLB (citrus greening) in citrus. This recommendation is based on the following:

1) BEAD reviewed FDACS's emergency request and determined that the recent introduction and rapid spread of ACP and HLB make this an urgent non-routine situation. BEAD concluded that there are no effective available alternatives for season long protection and that citrus growers in Florida have already suffered significant losses which are likely to continue without an effective solution. They agree with the assertion of FDACS that the long-term viability of the citrus industry in FL is in jeopardy from citrus greening disease.

2) HED concluded that there are no human health risk issues associated with the proposed uses on citrus in connection with these emergency exemptions. The toxicological, residue chemistry, dietary-exposure, and occupational/residential exposure assessments are adequate to support time-limited tolerances for residues of streptomycin in citrus fruit at 0.4 ppm and oxytetracycline for citrus fruit at 2 ppm and for dried citrus pulp at 6 ppm.

3) EFED reviewed the emergency exemption requests and stated that the maximum proposed application rates on citrus are similar to the maximum application rate of other currently registered rates apples and pears for both materials. EFED's assessment for the proposed use of streptomycin, determined that use of streptomycin on citrus in Florida may lead to chronic effects on mammals (RQ=11.6) and sensitive aquatic nonvascular plants (RQ=3.2). However, the mammal RQ is based upon the 2-year rat study with the only effect seen of decreased body weight gain. For oxytetracycline, EFED determined that the absolute RQ values for chronic exposure from the proposed use on citrus are well below the chronic risk LOCs of 1.0; however, there is uncertainty due to the non-definitive nature of the NOAEL used in the assessment.

4) Although the EFED assessments indicated a potential for adverse effects to listed species, the reviews included conservative assumptions and assume the maximum exposures contrary to real practices. Therefore, the exposures would likely be less thus reducing the potential for unreasonable adverse effects. Further, FDACS conducted a refined endangered/threatened species review and determined that no listed species co-occur in the proposed use area.

5) RD acknowledges the concerns associated with the use of antibiotics contributing to development of resistance in environmental microbes and impact to human or animal pathogens. However, RD notes a need to balance potential risks with the severity of the emergency situation and potential benefits for alleviating the situation. RD believes the situation to be an urgent emergency, jeopardizing the existence of Florida's citrus industry. While antibiotic use is not seen as a long-term solution, it may provide assistance in the interim while more viable long-term solutions are developed.

6) Monitoring for resistance among endemic microbes in orchards will be required as part of the authorization and CDC/FDA will be consulted for input as to methods and data to be gathered under the monitoring program. FDACS has indicated willingness to conduct monitoring as prescribed by EPA. EPA will also require additional restrictions focused on mitigating risks for resistance development, as outlined previously in this document. Additionally, FDACS indicates that good stewardship practices such as rotating chemistries and ensuring reservoirs of the disease are destroyed (i.e., unproductive trees) are high priorities.

7) This is the first year that requests for use of streptomycin and oxytetracycline have been requested under section 18 of FIFRA to help manage HLB in citrus. Tolerance petitions in support of section 3 registration of the uses are currently under review by the Agency with a targeted completion date in the third quarter of 2017.

V. CONCURRENCE:

Jack E. Housenger, Director
Office of Pesticide Programs

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